

REMARKS

A. The Amendments and the Status of the Claims

Claims 100, 127, and 412 have been amended to define the Applicants' invention with more precision and particularity. The claims, as amended, are supported by the specification and the original claims. No new matter has been added. Claims 1-99, 101, 103-126, 128-193, 201, 202, 204-209, 214-216, 229-293, 301, 302, 304-309, 330, 338-346, and 357-411 have been previously canceled without prejudice. Claims 100, 102, 127, 194-200, 203, 210-213, 217-228, 294-300, 303, 310-329, 331-337, 347-356, and 412 are pending.

B. Priority

The Examiner has stated that the effective priority date of the present application is May 1, 1996 (item 2 on page 2 of the Office Action). The Applicants submit that the correct priority date is June 7, 1995, not May 1, 1996, because the present application is a continuation-in-part application of, and claims priority to, the U.S. Patent Application No. 08/497,684 ("parent application") having the filing date June 7, 1995. The priority was properly claimed when the present application was originally filed (page 1, lines 4-8 of the application, as originally filed). The Examiner's position seems to be that the present application is only entitled to the benefit of its own filing date of May 1, 1996 and not that of the parent application, because the parent application does not satisfy the written description requirement of 35 U.S.C. § 112, paragraph 1, as applied to the currently pending claims.

The Applicants respectfully disagree. It is undisputable that a continuation-in-part application is entitled to have the filing date of the parent application as its own filing date, if:

(1) the co-pendency is properly maintained in a chain of applications claiming priority to one another, so as long as

(2) every limitation of the claims of the continuation-in-part application is disclosed in the parent application in such a way as to satisfy the requirements of 35 U.S.C. § 112, paragraph 1.

As previously shown (see, the response to a previous Office Action filed 09/28/05), the requirement of the co-pendency has been clearly satisfied. As to the requirement (2) above, it is submitted that every feature, element, limitation, and relationship therebetween, recited in the currently pending claims are adequately disclosed in the parent application. Therefore, the present application is entitled to the filing date of the parent application, i.e., June 7, 1995.

In particular, the Examiner has determined that to satisfy these requirements in the context of the present case, the assessment is to be made based on the combined features of the combined features of the claimed formulation, such as the claimed gas species in combination with the specific phospholipids, gas mixtures, linking groups of polymeric moiety covalently bound to the phospholipids and targeting ligand of proteins, peptides, steroids, etc. (see, item 5 on page 5 of the Final Office Action). The Applicants submit that the parent application does provide enough information so as to allow one skilled in the art to conclude that the Applicants were in possession of the invention under the standard proposed by the Examiner, and thus the written description requirements of 35 U.S.C. § 112, paragraph 1, are satisfied.

To elaborate, the claims of the present application are directed to formulations that include targeted gas-filled vesicles, where the gas is derived from a perfluorocarbon or sulfur hexafluoride, where the vesicles include a disulfide linkages-free phospholipid, covalently conjugated to a targeting ligand via a linking group.

The parent application clearly discloses that the Applicants were in possession of such vesicles (e.g., on page 8, lines 4-5) filled with a gas (e.g., on page 15, lines 14-15). Using both perfluorocarbons and sulfur hexafluoride to fill the vesicles is also disclosed in the parent application (page 16, lines 8-9 and claim 6). Furthermore, using phospholipids is likewise disclosed in the parent application (page 9, lines 16-17), as is using disulfide-free linkages (e.g., using amide, ester, thioester, ether, or amino linkages, page 48, lines 20-24 and lines 34-36 of the parent application).

In addition, claims of the current application require that the linking group is a hydrophilic polymer such as PEG, polypropylene glycol, polyvinylalcohol, polyvinylpyrrolidone, and copolymers thereof. Using such polymers is disclosed on page 38, line 21 (hydrophilic polymer in general) and on page 37, line 37 through page 38, line 8 (examples of specific hydrophilic polymers). Finally, claims of the present application require the presence of lipid-linking group-targeting ligands, such as proteins, peptides, saccharides, steroids, steroid analogs, bioactive agents and genetic material. Using a lipid-linking group-targeting ligand is also disclosed in the parent application (page 48, lines 12-18), as is using specific ligands (see, page 8, lines 9-15 and page 43, line 10 through page 44, line 18 of the parent application).

In view of the foregoing, it is the Applicants' position that the claims of the present application are fully supported by the disclosure of the parent application. Accordingly, it is submitted that the present continuation-in-part application is entitled to the priority date of the parent application, i.e., June 7, 1995.

C. Rejections Under 35 U.S.C. § 103(a)

Claims 100, 102, 127, 194-200, 203, 210-213, 217-220, 294-300, 303, 310-317, 326, and 412 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,620,689 to Allen, in view of U.S. Patent No. 4,853,228 to Wallach, U.S. Patent No. 5,643,553 to Schneider and U.S. Patent No. 5,648,098 to Porter (item 9 on page 5 of the Office Action). Also, claims 318-325, 327-329, 331-337, and

347-356 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Allen, in view of Wallach, Schneider and Porter and further in view of U.S. patent No. 5,656,442 to Ginsburg (item 21 on page 8 of the Office Action). These rejections are respectfully traversed.

The basic criteria that must be satisfied to establish a *prima facie* case of obviousness were discussed previously (see the response to a previous Office Action filed 09/28/05). The Applicants respectfully submit that these criteria have not been satisfied in this case because none of the cited references, either alone or in combination, disclose or suggest every limitation of claims 100, 127, and 412.

Specifically, each of claims 100, 127, and 412, now recites vesicles including “a lipid covalently conjugated to a targeting ligand via a linking group, wherein said linking group is a hydrophilic polymer.” In addition each of claims 100, 127, and 412, also recites “gas-filled vesicles” wherein the gas is a “perfluorocarbon or sulfur hexafluoride.” The references cited by the Examiner, or combinations thereof, neither disclose nor suggest such limitations.

More specifically, neither Allen nor Wallach describe gas-containing vesicles or liposomes that include a gaseous ultrasound agent. Ginsburg fails to cure this deficiency, by not disclosing that gas-filled vesicles can be used. All Ginsburg teaches is only the use of some targeting agents. Therefore, the Examiner needs to combine the teachings of Allen, Wallch and Ginsburg with those of Schneider, since, according to the Examiner, Schneider describes gas-filled microbubbles (see, item 12, page 6, lines 1-2 of the Office Action).

However, as conceded by the Examiner, Schneider does not describe the use of a perfluorinated gaseous liposome covalently bound to a targeting ligand (see, item 14, page 6, lines 14-16 of the Office Action). Nor does Schneider describe the use sulfur hexafluoride gaseous liposome covalently bound to a targeting ligand.

Therefore, Allen, Wallach, Schneider, Ginsburg, or any combination thereof, fail to explicitly disclose perfluorocarbon or sulfur hexafluoride-filled vesicles covalently bound to a targeting ligand. To overcome this problem, the Examiner has proposed to modify the teachings of Schneider to read them as if they included perfluorocarbon-filled vesicles covalently bound to a targeting ligand (see, item 14, page 6, lines 18-20 of the Office Action).

One rationale proposed by the Examiner to justify such modification is the existence of Porter the disclosure of which teaches the use of perfluorocarbons. However, Porter is not available as the proper prior art reference, because the present application has the priority date of June 7, 1995, while the earliest reference date for Porter is October 17, 1995. Therefore, the present application pre-dates Porter, and accordingly Porter is not prior art against the present application, and does not qualify as a valid 35 U.S.C. § 103 reference.

Even if Porter were available as a prior art reference, the Applicants submit that the modification of Schneider as proposed by the Examiner would be improper because there is nothing in Schneider, or in Allen, Wallach, or Ginsburg, or in any combination of these four references providing suggestion that might motivate one skilled in the art to prepare such formulation. These references are simply silent in that regard.

It is submitted that it is indeed unclear from the face of Schneider, Allen, Wallach, or Ginsburg why these references should or could be combined. The only reason given by the Examiner is that "Schneider provides ample motivation in the art and reasonable expectation of success for preparing a perfluorinated gaseous liposome that is covalently bound to a targeting ligand via a PEG linker" (see, item 14, page 6, lines 18-20 of the Office Action). It is respectfully submitted that this statement is conclusory and does not explain the rationale for the conclusion. While it is possible to make a perfluorinated gaseous liposome described by the Examiner, just a possibility of the existence of an embodiment comprising features disclosed in several references is not in

itself sufficient to provide motivation for making such a combination. More is required, e.g., showing that combining the references is desirable and/or beneficial in some way, and such showing must come from the references themselves, not from speculation.

The law requiring a suggestion or motivation in order to be able to combine and/or modify references is well established. When, as in this case, the motivation to combine the teachings of the references is not immediately apparent, it is the duty of the examiner to explain why the combination or modification of the teachings is proper. *Ex parte Skinner*, 2 USPQ2d 1788 (Bd. Pat. App. & Inter. 1986). The Applicant respectfully submits that the Examiner has not fulfilled this duty.

It is also well established that in making rejections over the prior art, the Patent Office "may not, because it may doubt that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis." *In re Warner*, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), *cert. denied*, 389 U.S. 1057 (1968). It is submitted that the fact that the Examiner's has not provided a reasoned factual statement explaining the desirability of combining the teachings of the references amounts to making such "unfounded assumptions or hindsight reconstruction."

Just because it is possible to modify Schneider to make a perfluorinated gaseous liposome, does not mean that Schneider itself, or its combination with other cited references can be used to reject any invention using perfluorinated gaseous liposome as obvious. Accordingly, the Applicants respectfully submit that the teachings of Schneider, Allen, Wallach, or Ginsburg are not properly combinable nor is Schneider properly modifiable due to lack of motivation to do so.

In view of the foregoing, it is respectfully submitted that claims 100, 127 and 412 are patentably distinguishable over the references cited by the Examiner because neither any of the references nor any combination thereof teaches or suggests every element of claims 100, 127, or 412.. All other claims depend, directly or indirectly, on either claim

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100 or claim 127, and are allowable for at least the same reason. Reconsideration and withdrawal of the rejection are respectfully requested.

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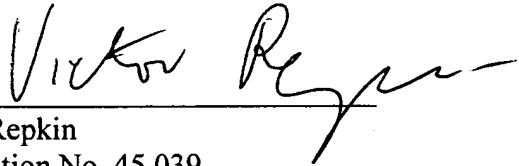
CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

Check number 583070 in the amount of \$395.00 is enclosed as payment for the Request for Examination fee. No other fee is believed to be due in connection with filing this submission. However, the Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A duplicate copy of this Transmittal sheet is enclosed.

Respectfully submitted,

Date: August 25, 2006



Victor Repkin
Registration No. 45,039
Telephone: (858) 638-6664
Facsimile: (858) 677-1465

DLA PIPER RUDNICK GRAY CARY US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer Number 28213